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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/420,433	10/12/1999	DAVID SIDRANSKY	JHU1180-1	2810

7590 12/13/2007

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EXAMINER	
JOHANNSEN, DIANA B	
ART UNIT	**PAPER NUMBER**
1634	

MAIL DATE	DELIVERY MODE
12/13/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/420,433	SIDRANSKY, DAVID	
	Examiner	Art Unit	
	Diana B. Johannsen	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 September 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,7-12,14,18-22 and 24-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,7-12,14,18-22 and 24-26* is/are rejected.

7)☒ Claim(s) *20-22 and 24* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on September 25, 2007 has been entered.

2. Claims 1-4, 11-12, 18-22, and 25-26 have been amended. Claims 1-4, 7-12, 14, 18-22, and 24-26 are now pending and under consideration.

Claim Objections

3. Claims 20-22 and 24 are objected to because of the following informalities: in claim 20, the "isolating" and "extracting" steps are not separated by punctuation. This objection could be overcome by inserting a semicolon at the end of the "isolating" step. Appropriate correction is required.

Claim Rejections - 35 USC § 112, first paragraph

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-4, 7-12, 14, 18-22, and 24-26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable

one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (A) the breadth of the claims; (B) the nature of the invention; (C) the state of the prior art; (D) the level of one of ordinary skill; (E) the level of predictability in the art; (F) the amount of direction provided by the inventor; (G) the existence of working examples; and (H) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (*MPEP* 2164.01(a)).

Claims 1-4 and 7-11 are drawn to methods in which a "target neoplastic nucleic acid" selected from APC, DCC, NF1, NF2, RET, VHL, and WT-1 is detected in a tumor margin tissue specimen that is "external to a primary neoplasm" and "histologically normal." Claims 12 and 14 are drawn to methods in which a "target neoplastic nucleic acid" that is selected from APC, DCC, NF1, NF2, RET, VHL, and WT-1 is detected in a surgical margin that is "histologically normal" as an indicator of metastases. Claim 18 encompasses detection of such a target neoplastic nucleic acid in a "tissue specimen which is external to a primary neoplasm" and "histologically normal," while claim 19 requires the presence of such a nucleic acid in a "tumor margin tissue specimen" that "appears histologically normal." Claims 20-22 and 24 are drawn to methods in which a "target neoplastic nucleic acid" selected from APC, DCC, NF1, NF2, RET, VHL, and

WT-1 is detected in a "lymph node tissue specimen" that is "external to a primary neoplasm" and which "appears histologically normal." Claims 25-26 are drawn to methods in which a "target neoplastic nucleic acid" that is selected from APC, DCC, NF1, NF2, RET, VHL, and WT-1 is detected in tissue from a lymph node that is "external to a primary neoplasm" and "appears histologically normal" as an indicator of metastases.

It is unpredictable as to whether one of skill in the relevant art could use the invention of the instant claims. The claims as written require that each of the "target neoplastic" nucleic acids recited therein may be detected in tumor margins and lymph node tissues that are or appear "histologically normal." However, the specification only exemplifies the detection of a different target nucleic acid, p53, in surgical margins and lymph nodes that appear histologically normal by light microscopy in patients afflicted with head and neck squamous cell carcinoma (see Examples 1-4, as well as Figures 2-5 and 7-9). Applicant's specification does not provide any evidence that mutated versions of any of the nucleic acids recited in the instant claims were -- or can be -- detected in any type of sample (from any type of patient, with any type of cancer) that is or that appears "histologically normal." Many types of microscopy were available for use by those of skill in the art at the time the invention was made, and additional techniques such as staining and labeling may be employed with microscopy to increase its sensitivity. Given the absence of evidence and data provided in the specification regarding the detection of the nucleic acids of the claims in any type of "histologically normal' sample, it is completely unpredictable as to whether said nucleic acids may in

fact be detected by the methods of the claims in such samples. With further regard to claims 12 and 25 and claims dependent therefrom, it is further noted that the specification is also silent with regard to detection of any of these nucleic acids in any type of "histologically normal' sample as an indicator of metastasis. Lacking guidance from the specification, one of skill in the art may look to the teachings of the art for further guidance and enablement of a claimed invention. However, in the instant case, the prior art is also silent with respect to any teachings that mutant versions of any of the genes of the instant claims may be detected in, e.g., surgical margins or lymph nodes that are or appear "histologically normal." The closest prior art reference, Nees et al (Cancer Research 53(18):4189-4196 [9/1993]), discloses that mutated p53 nucleic acids were detected in tumor margin specimens obtained from patients with head and neck cancers (see, e.g., Table 3, p. 4191, 4193). However, Nees et al note that their findings with p53 suggest that multiple tumor development may be a "multifocal polyclonal process" rather than a monoclonal process "initiated by lateral movement" of premalignant cells, and state that "At present, there is no information as to which other tumor suppressor genes" might be among those that (along with p53) undergo genetic changes contributing to head and neck cancer progression (see page 4195, last paragraph). Thus, the teachings of the prior art suggest the manner in which cells containing the mutant nucleic acids of the claims might arise in lymph nodes and/or tumor margin tissues is not clear. Further, the teachings of the specification also support a conclusion that p53 is not analogous or equivalent to the genes of the present claims; for example, page 11 of the specification teaches that p53 mutations are found

in "50% of all cancers," while showing that the genes of the present claims are associated with particular cancer types.

Given the lack of evidence in both the specification and in the art with regard to how (or even whether) cells comprising the nucleic acids of the claims might spread to lymph nodes and/or tumor margin tissues, it cannot be predicted whether specimens taken from these locations that were found to contain detectable levels of such "target neoplastic" nucleic acids would in fact appear histologically normal. As noted above, many types of microscopy were available for use by those of skill in the art at the time the invention was made, and additional techniques such as staining and labeling may be employed with microscopy to increase its sensitivity. While it is certainly possible that such specimens might be identified, this question could only be resolved by further experimentation. Given the high level of skill of one skilled in the relevant art, it is clearly within the ability of such an artisan to conduct such further experimentation – however, the outcome cannot be predicted, and it is in fact possible that no quantity of experimentation would be sufficient to enable the claims. As it is unknown as to whether any quantity of experimentation would actually be sufficient to enable the practice of the claimed invention, it would clearly require an undue quantity of experimentation to use the invention of the instant claims.

The response of September 25, 2007 traverses the rejection on the following grounds. The response references advantages of the invention that are discussed in the specification at page 4, and notes that the methods of the invention "provide the advantage of detecting the metastasis of a small number of tumor cells into

normal tissue before such cells are able to grow into a tumor that is visible by standard histological methods." Applicant argues that the specification "provides abundant guidance for the practice of the claimed methods as well as a detailed working example," citing the evidence presented in the specification that "mutant p53 nucleic acid present in metastatic tumor cells can be detected in tissues (e.g., tumor surgical margin and lymph nodes) containing a small number of such metastatic tumor cells, even though such tissues appear histologically normal." The response urges that this example provides a "general teaching" that may be extrapolated to the genes of the present claims, and that "one of skill in the art would have reasonably expected that mutations in any of the other recited tumor suppressor genes...could similarly be detected in histologically normal tissue containing metastatic tumor cells from the primary tumor." Applicant argues that "the skilled artisan simply need know whether one or more of the target neoplastic nucleic acids is present in a mutated form in the primary neoplasm," and as this was known with regard to the genes set forth in the claims, the invention claimed is enabled. Regarding the Nees et al reference cited by the examiner, the response urges that this reference is "not relevant" to the claimed methods, as it pertains to a possible multifocal process involved in the development of "different p53 mutations in primary and secondary" head and neck tumors, while the claims are drawn to methods in which the same mutation present in a primary tumor is detected in the histologically normal tissue.

These arguments have been thoroughly considered but are not persuasive. First, it is noted that the examiner has not disputed the fact that early detection of

cancer in histologically normal tissues is advantageous; rather, the instant rejection was advanced because applicant has not established that, at the time the invention was made, the methods claimed could actually be practiced without undue experimentation. The evidence provided in the specification with regard to p53 is again acknowledged; however, the instant claims recite and are limited to genes other than p53 for which no such data has been provided. As was indicated in the prior rejection (and is reiterated above), the teachings of the specification and of the prior art do not support a conclusion that one skilled in the art could have practiced applicant's methods with respect to the genes now recited in the claims. Neither the specification nor the prior art establish that one could successfully substitute one or more of the genes of the claims for p53 in applicant's methods. On the contrary, as noted above, the specification teaches that p53 is associated with a wide variety of different cancers (rather than a limited number of particular types), and the prior art of Nees et al teaches "At present, there is no information as to which other tumor suppressor genes" might be among those that (along with p53) undergo genetic changes contributing to head and neck cancer progression (see page 4195, last paragraph). While applicant argues that the Nees et al reference is "not relevant" to the claimed invention, it is again noted that the prior art is silent regarding the detection of the genes of the instant claims in "histologically normal" samples. The Nees et al reference is in fact relevant in that it teaches the detection in a "histologically normal" sample of another nucleic acid (p53) that was also assayed by Applicant, and in that it establishes the general state of the art, and the unpredictability of this particular art area, at the time applicant's invention

was made. Further, to the extent that the Nees et al reference may teach that the mechanism by which p53-related tumors develop and/or progress differs from the mechanism asserted by applicant with regard to the genes of the claims, the reference further supports a conclusion that applicant's own findings with p53 may not be relevant to other genes, such as those recited in the claims. Accordingly, Applicant's arguments are not persuasive.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claim 19 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 19 is indefinite because it is unclear whether the claim is drawn to a method "for detecting a mammalian target neoplastic nucleic acid having a mutant nucleotide sequence in a tumor margin tissue specimen" as indicated in the preamble of the claim, or to a method of detecting such a nucleic acid in any tissue specimen that "appears histologically normal," as suggested by the method steps of the claim. In particular, it is noted that the sample isolated in the "isolating" step is described as a "tissue specimen wherein the tissue specimen appears histologically normal;" there is no indication that the specimen must be obtained from a tumor margin, and no reference back to the "tumor margin tissue specimen" mentioned in the claim preamble.

Thus, it is not clear whether the method is or is not limited to tumor margin tissue specimens.

Conclusion

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Diana B. Johannsen whose telephone number is 571/272-0744. The examiner can normally be reached on Monday and Thursday, 7:30 am-4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached at 571/272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Diana B. Johannsen
Primary Examiner
Art Unit 1634